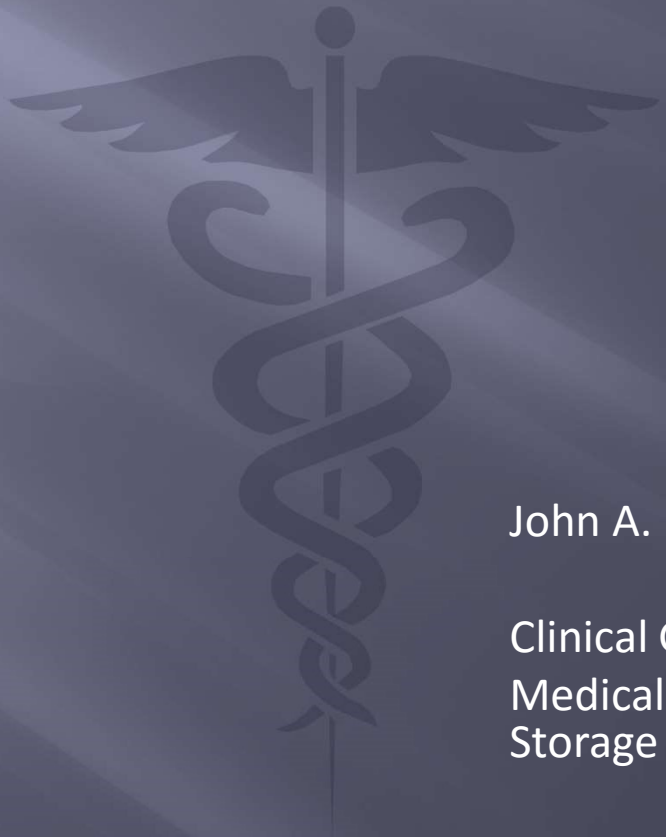
MEDICAL SPECIALISTS



John A. Bernat, MD, PhD

Clinical Geneticist,
Medical Director of the Iowa Lysosomal Storage Disorders Center, University of Iowa

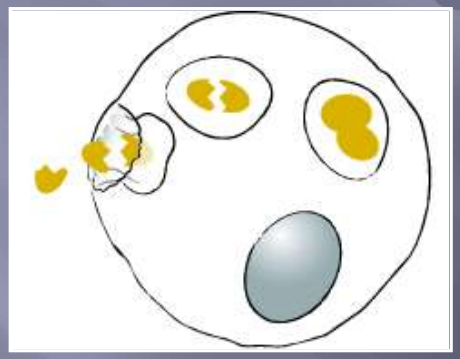
Iowa Lysosomal Storage Disorders Center

- Evaluation and treatment of lysosomal storage disorders
  - Fabry disease
  - Gaucher disease
  - Mucopolysaccharidoses
    - Hurler, Hunter, Sanfilippo, Morquio, Maroteaux-Lamy syndromes
  - Pompe disease
  - Lysosomal acid lipase deficiency
- Multidisciplinary team
  - Clinical geneticist – John Bernat, MD, PhD
  - Physician assistant – Myrl Holida, PA-C
  - Specialists – nephrologists, cardiologists, neurologists, orthopedic surgeons, anesthesiologists, otolaryngologists

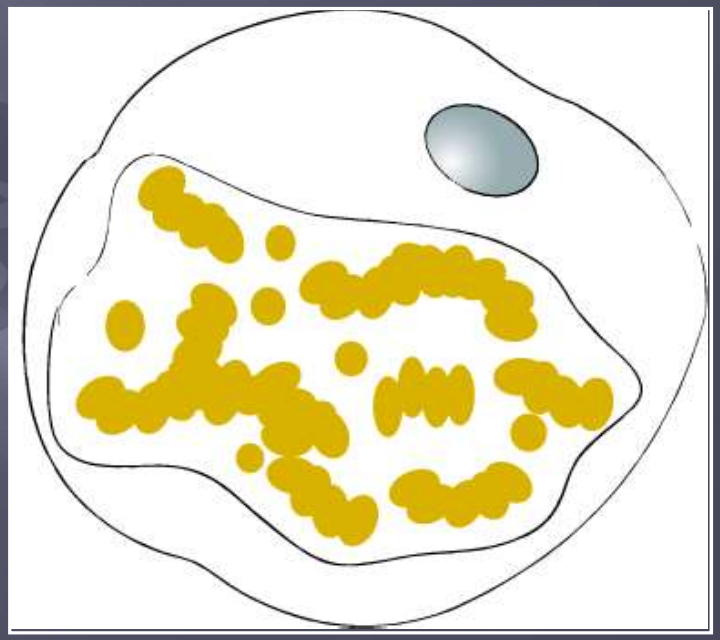
Iowa Lysosomal Storage Disorders Center

- Long-term management
  - Enzyme replacement therapy – IV infusions every 1-2 weeks
  - First several infusions in Iowa City; can transition to local/home infusions
  - Stable patients seen in Iowa City about once yearly
- Clinical research program
  - 3 active clinical trials involving pegunigalsidase, a novel treatment for Fabry disease
  - Previous clinical trials with Fabry and Gaucher disease patients
  - Rare disease registries

Lysosomal storage disorders



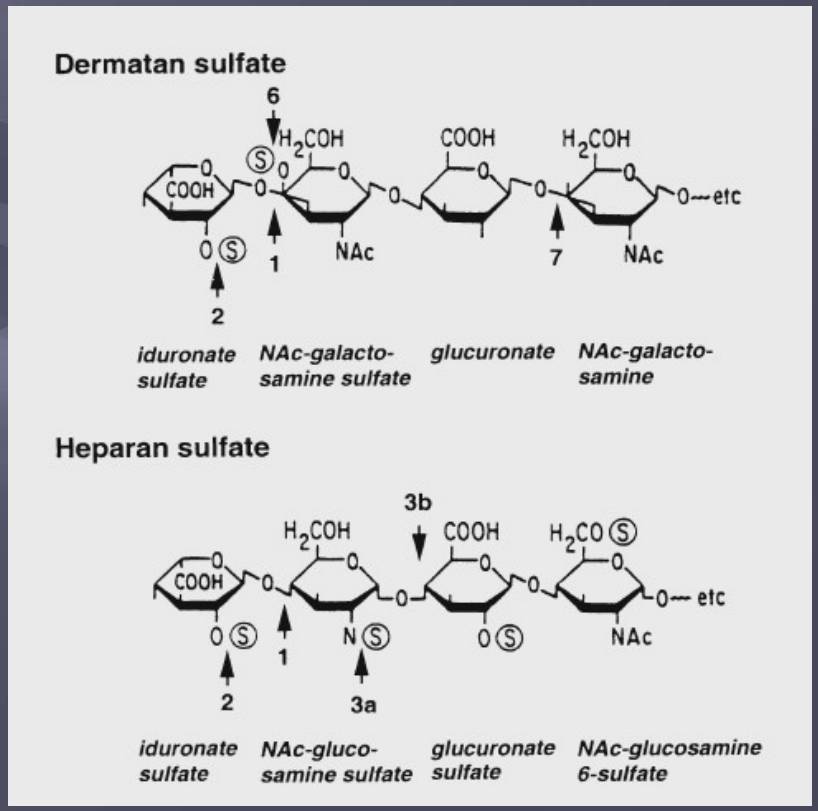
Normal Cell



Abnormal Cell

MPS I

- Mucopolysaccharidosis type I
  - Hurler, Hurler-Scheie, Scheie syndromes
- Defect in alpha-L-iduronidase
  - Needed for breakdown of two glycosaminoglycans (dermatan sulfate, heparin sulfate)
- GAGs: highly-sulfated sugar chains bound to core proteins
  - Important components of connective tissue (cartilage, blood vessel walls)

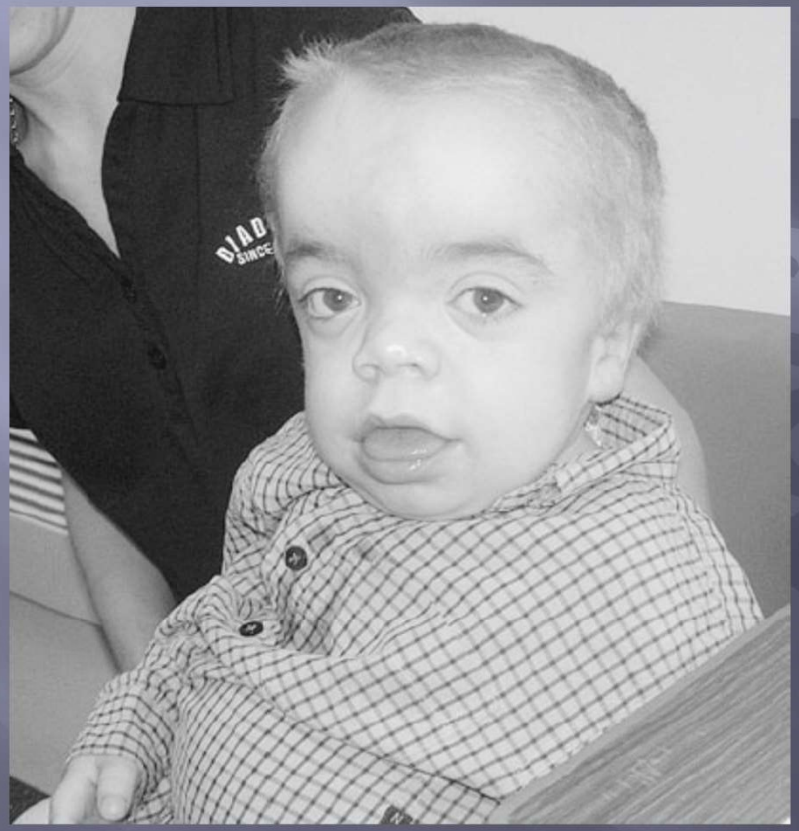


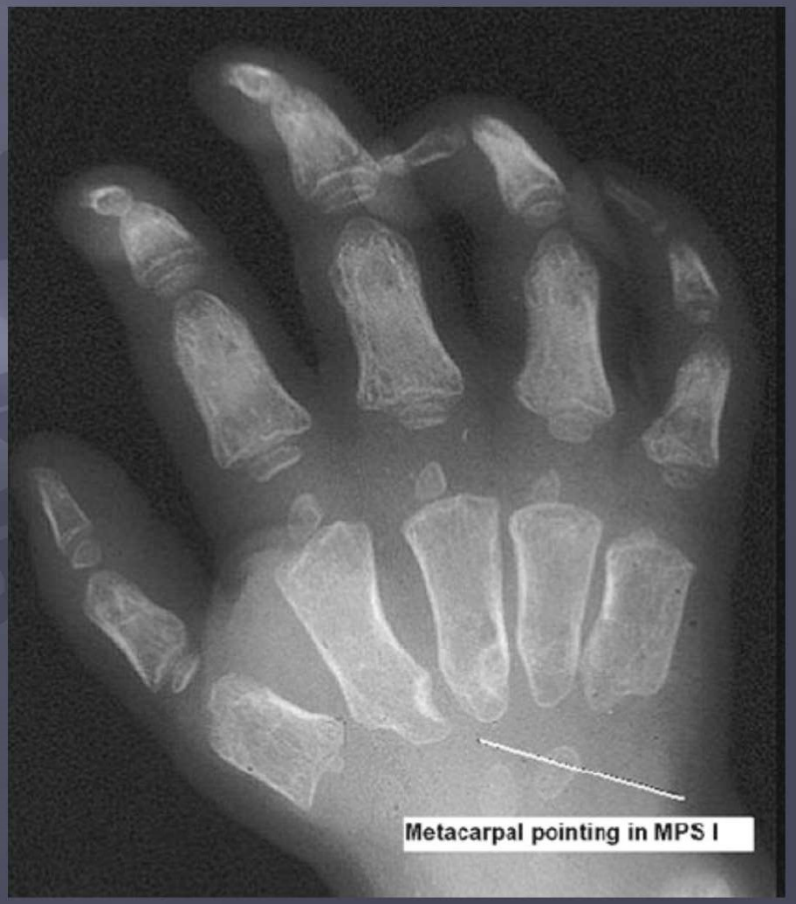
Saudubray et al, Fig. 40.1

Severe MPS I (Hurler syndrome, MPS IH)

- Mean age of diagnosis: 9 months
- Most diagnosed by 18 months
- Usually no physical findings at birth
- Initial symptoms: frequent URIs, umbilical/inguinal hernias
- Disease progression: enlargement of liver/spleen, bone deformities, short stature (linear growth stops around age 3), coarsening of facial features, hearing loss, corneal clouding, airway obstruction, heart disease (valvular disease, cardiomyopathy), developmental delay
- Untreated: death by age 8-10
- Prevalence: 1:100,000

Severe MPS I (Hurler syndrome, MPS IH)





Saudubray et al, Fig. 40.2, 40.5

Severe MPS I (Hurler syndrome, MPS IH)

Nyhan et al, Fig. 76.1, 76.2, 76.3, 76.4

Attenuated MPS I (Hurler-Scheie/MPS IH-S, Scheie/MPS IS)

- Disease onset: age 3-10
- Variable phenotype: similar conditions, but varying degrees of involvement
- Normal intellect or mild delays
- Untreated: death in 2nd/3rd decades… to normal life span
- Prevalence: 1:500,000

Treatment

- Enzyme replacement therapy (ERT)
  - Laronidase (Aldurazyme) – BioMarin/Genzyme, FDA-approved in 2003
  - 100 U/kg (0.58 mg/kg) IV every week
  - Does not cross blood-brain barrier; no effect on CNS disease
- Hematopoietic stem cell transplant ("bone marrow transplant")
  - Studied before ERT was available
  - Seems not to help skeletal and cardiac manifestations
  - May slow cognitive impairment?
    - If transplant occurs before significant developmental delay (e.g. 12-18 months)

NBS for MPS I

- Reasons for:
  - Arrive at the correct diagnosis much more quickly
  - Can start treatment (enzyme replacement therapy, HSCT) before onset of symptoms
  - Early HSCT (before age 18 months) is important for best neurocognitive outcomes
- Reasons against:
  - Identification of false positives (including “pseudodeficiency” individuals)
  - Identification of attenuated MPS I patients
  - Cost of treatments

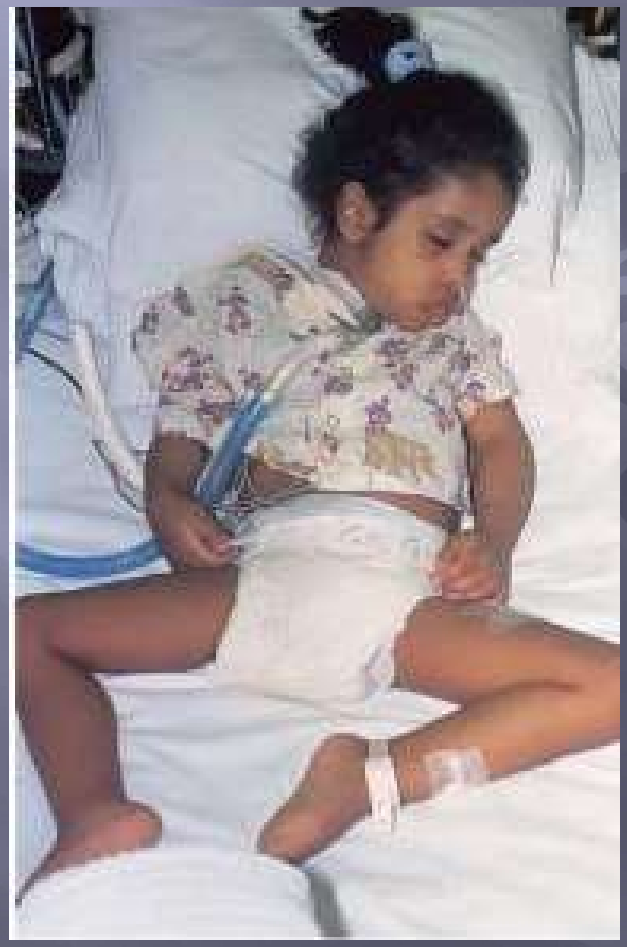
Pompe disease

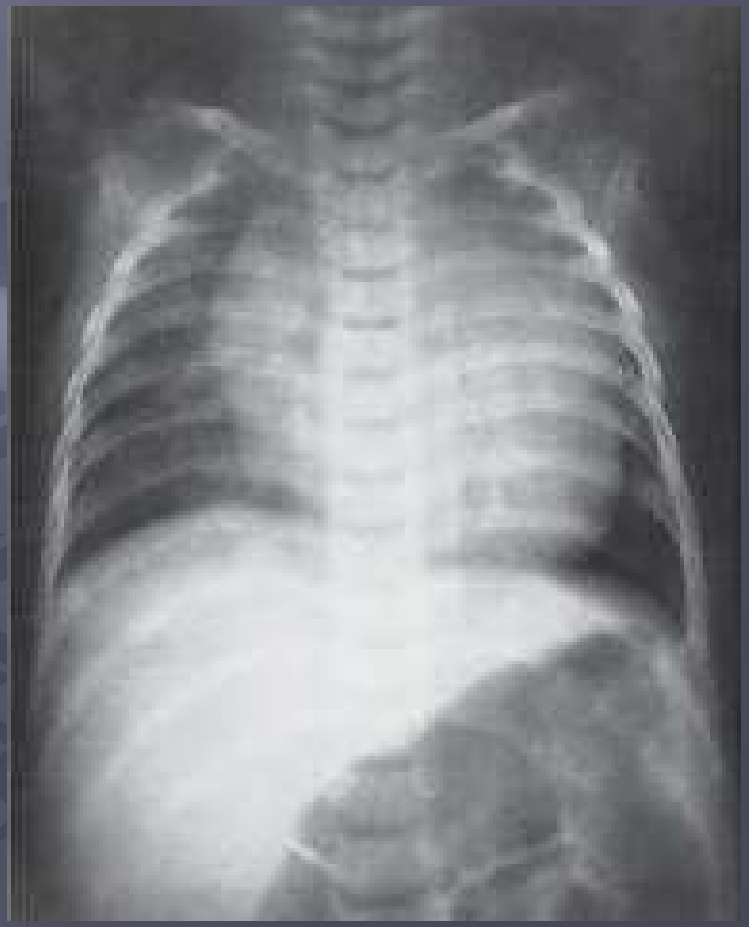
- Glycogen storage disease type II
- Deficiency in lysosomal acid alpha-glucosidase (GAA)
  - AKA acid maltase deficiency
- Two forms:
  - Infantile-onset
    - Enzyme activity <1% of normal controls
  - Late-onset (includes childhood, juvenile, adult-onset)
    - Enzyme activity 2-40% of normal controls

Infantile-onset Pompe disease

- Typically presents in first 2 months of life
  - Low muscle tone, feeding problems, poor weight gain, difficulty breathing
  - Chest x-ray: heart enlargement
- Without treatment: fatal in first year
  - Hypertrophic cardiomyopathy
  - Eventually leads to heart failure, death

Infantile-onset Pompe disease





Nyhan et al, Fig. 60.6, 60.8

Late-onset Pompe disease

- Primarily a muscle disease; heart is less affected
- Variable phenotype
  - Initial symptoms from late infancy to adulthood
  - Progress muscle weakness – can resemble muscular dystrophy
  - Eventually involves respiratory muscles
    - Respiratory insufficiency: primary cause of death in adults
  - Rarely: arteriopathy (glycogen deposition in vascular smooth muscle)

Treatment

- Enzyme replacement therapy
  - US: Myozyme (2006)/Lumizyme (2010) – Genzyme
  - Recombinant human GAA
  - Dose: 20-40 mg/kg IV every 2 weeks
- CRIM-negative patients: immunomodulation
  - Rituximab, methotrexate, IVIG

NBS for Pompe disease

- Reasons for:
  - Arrive at the correct diagnosis much more quickly
  - Can start treatment (ERT) before onset of symptoms and/or serious illness
- Reasons against:
  - Identification of false positives (including “pseudodeficiency” individuals)
  - Identification of late-onset Pompe disease patients
  - Cost of treatments

Patient presentation

- Jean and Jason Kelly

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